RESULTS FROM THE MYRIAM REGISTRY

FIRST GLANCE ON OUTCOME IN ROUTINE CARE OF PATIENTS WITH MULTIPLE MYELOMA IN GERMANY

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INTRODUCTION

Many advances have been made recently in the treatment of multiple myeloma (MM) with the approval of new treatments. Patients in routine care differ from those in clinical trials, in which various criteria limit inclusion. Registries such as MYRIAM are an ideal source to describe effectiveness of treatment and outcome in routine care.

PATIENTS AND METHODS

MYRIAM is a prospective, longitudinal, multicenter registry on patients with MM in Germany. Between 2017 and 2026, about 2,200 patients with MM starting their first- (1L), second- (2L) or third-line (3L) systemic treatment will be recruited in 150 sites (hospitals, office-based practices) and followed for a maximum of 5 years. The study was reviewed by ethics committees and is registered at clinicaltrials.gov (NCT03308474). Recruitment goal for patients enrolled in first-line treatment was reached in October 2021. Here, we present first outcome data from start of first-line treatment (database cut: 30.09.2022). The sample for analyses of outcome parameters was defined as all patients with start of first-line treatment at least two years prior to database cut ("outcome sample"), to increase the length of minimum follow-up and reduce bias in outcome data.

RESULTS

In total, 1,482 patients had been recruited at start of first-line treatment, whereof 894 patients (60%) were not planned for stem cell transplantation (non-SCT) and 588 (40%) were scheduled for SCT with details on SCT induction available for 575 patients.

Patients not planned for SCT were older (median 78 / 63 years) and more often had comorbidities (90% / 75%) than patients scheduled for SCT (Table 1). Overall, patients were predominantly in good general health at start of treatment: non-SCT: 20 % ECOG 0 / 45 % ECOG 1; planned SCT: 44 % ECOG 0 / 39 % ECOG 1 **(Table 1).**

Patients not planned for SCT

First-line treatment (start in 2017-2021) in patients not planned for SCT were mostly bortezomib (no CD38-antibody)-containing protocols (n=468/894, 52%) or anti-CD38-antibody/bortezomib-based protocols (n=301/894, 34%) **(Figure 1)** with BOR/Dexa (n=174/894, 19%) and DARA/LENA/Dexa (n=124/894, 14%) being the most frequently used combinations. With the approval of daratumumab for first-line treatment (non-SCT) in mid-2018, anti-CD38-mAB-protocols increased from 8% (2018) to 54% (2021), whereas BOR-protocols decreased from 74% (2018) to 41% (2021) **(Figure 1)**.

For first-line non-SCT, best response data were available for 85% (n=538/632) of patients; for the remaining patients, the majority of first-line treatment were still ongoing. The overall response rate (partial response or better) for patients not planned for SCT was 49% (n=264) with respect to all patients with available data on best response (n=538), or 42% with respect to all patients of the analyzed outcome sample (n=632, **Figure 3**).

Overall, 29% (n=255/894) had already received a second-line treatment. 17% (n=156/894) had died without receiving a second-line treatment and for 41% first-line treatment was either ongoing (n=270/894, 30%) or patients were on a drug holiday (break of treatment; (n=98/894, 11%) **(Table 2)**. For the remainder, documentation had been completed, mostly due to loss during follow-up.

Median progression-free survival (PFS) from start of first-line treatment was 19.0 months [95% CI 16.8-22.4] **(Figure 5)**.

Median overall survival (OS) was not reached; the 2-year OS rate was 74.3% [95% CI 70.3-77.7] **(Figure 7)**.

Patients scheduled for SCT

First-line treatment (2017-2021) for SCT induction were mostly bortezomib (no CD38-antibody)-containing protocols (78%, n=451/575) or anti-CD38-antibody/bortezomib-based protocols (18%, n=101/575) **(Figure 2)** with BOR/CYC/Dexa (n=307/575, 53%) being the far most frequently used combination. However, with the approval of daratumumab for first-line treatment (SCT induction) in 2020, anti-CD38-mAB-protocols increased from 23% (2020) to 44% (2021), whereas BOR-protocols decreased from 72% (2020) to 54% (2021)

The overall response rate (partial response or better) of SCT induction was 73% (n=261) with respect to all patients with available data on best response (n=357), or 67% with respect to all patients of the analyzed outcome sample (n=389, **Figure 4**).

In 81% (n=316/389) the transplantation was performed, whereas for 11% (n=43/389) the transplantation was cancelled; for the remainder data were not available (data not shown).

Among patients scheduled for SCT, 22% (n=129/588) had already received a second-line treatment. 4% (n=23/588) had died without receiving second-line treatment and for 69% first-line treatment was either ongoing (n=291/588, 49%) or patients were on a drug holiday (n=116/588, 20%) **(Table 2)**. For the remainder, documentation had been completed, mostly due to loss to follow-up.

Median progression-free survival (PFS) from start of first-line treatment was 42.3 months [95% CI 39.0-49.1] **(Figure 6)**.

Median overall survival (OS) was not reached; the 2-year OS rate was 92.0% [95% CI 88.6-94.4] (planned SCT) **(Figure 8)**.

CONCLUSION

MYRIAM serves as a reference on outcome in routine care of unselected patients with MM in Germany. Previous publications have shown that new treatment options are quickly implemented by MYRIAM sites. Here, the obvious increase of daratumumab-based treatments in first-line treatment indicates a rise as the new standard of care for patients with newly diagnosed MM in real world. First data on PFS and OS from first-line treatment indicate that patients in routine care have similar outcomes compared to data from published clinical trials, especially when comorbidities and inferior performance status are considered.

If the implementation of newly approved treatments translates into an improved long-term outcome and overall prognosis will be evaluated after longer follow-up.

Table 1: Patient characteristics at start of first-line treatment

	Patients not planned for SCT (non-SCT)	Patients scheduled for SCT (planned SCT)	Patients with SCT induction (SCT-IND)
Patients (N)	**894**	**588**	**575**
Sex			
Male n (%)	490 (54.8%)	348 (59.2%)	342 (59.5%)
Female n (%)	404 (45.2%)	240 (40.8%)	233 (40.5%)
Age at start of first-line-treatment			
Mean ± StD (years)	76.4 ± 7.34	61.7 ± 8.32	
Median (years)	77.6	62.9	62.9
25-75% quantile (years)	72.2 - 81.1	57.1 – 67.7	
<65 years / ≥ 65 years n (%)	68 (7.6%) / 826 (92.4%)	357 (60.7%) / 231 (39.3%)	
<70 years / ≥ 70 years n (%)	155 (17.3%) / 739 (82.7%)	504 (85.7%) / 84 (14.3%)	
Comorbidities			
Yes n (%)	803 (89.8%)	442 (75.2%)	432 (75.1%)
No n (%)	89 (10.0%)	145 (24.7%)	142 (24.7%)
Missing n (%)	2 (0.2%)	1 (0.2%)	1 (0.2%)
Charlson comorbidity index (CCI) [0-24]			
CCI 0 n (%)	558 (62.4%)	461 (78.4%)	453 (78.8%)
CCI 1 n (%)	133 (14.9%)	60 (10.2%)	57 (9.9%)
CCI ≥ 2 n (%)	201 (22.5%)	66 (11.2%)	64 (11.1%)
Missing n (%)	2 (0.2%)	1 (2.2%)	1 (0.2%)
ECOG performance status			
ECOG 0 n (%)	181 (20.2%)	256 (43.5%)	251 (43.7%)
ECOG 1 n (%)	403 (45.1%)	231 (39.3%)	226 (39.3%)
ECOG ≥ 2 n (%)	192 (21.5%)	47 (8.0%)	44 (7.7%)
Unknown n (%)	98 (11.0%)	40 (6.8%)	40 (7.0%)
Missing n (%)	20 (2.2%)	14 (2.4%)	14 (2.4%)
CRAB [a]			
C - Hypercalcemia n (%)	95 (10.6%)	80 (13.6%)	
R - Renal insufficiency n (%)	139 (15.5%)	74 (12.6%)	
A - Anemia n (%)	466 (52.1%)	272 (46.3%)	
B – Bone disease (osteolytic or diffuse bone destruction) n (%)	474 (53.0%)	403 (68.5%)	

N: Patients enrolled for first-line treatment (prospective documentation for first line).
[a] Multiple answers possible.
CRAB criteria:
C: Hypercalcemia: Serum calcium: > 2,75 mmol/L (> 10,511 mg/dL) or 0,25 mmol/L (> 1mg/dL) above upper normal value.
R: Renal insufficiency: Creatinine clearance below 40 mL/min or serum creatinine above 177 µmol/L (above 2 mg/dL).
A: Anaemia: Hemoglobine < 10 g/dL or > 2 g/dL below lower normal value.
B: Bone disease: One or more osteolytic lesions (reports according to computer tomography (CT), positron emission tomography / computer tomography (PET-CT), magnetic resonance imaging (MRI) or X-ray).

Table 2: Patient follow-up status as second-line treatment

	Patients not planned for SCT (non-SCT)	Patients scheduled for SCT (planned SCT)
Patients (N)	**894**	**588**
Patient status at second-line treatment		
Treatment received n (%)	255 (28.5%)	129 (21.9%)
Potential for respective line of treatment n (%)	368 (41.2%)	407 (69.2%)
Documentation completed prior to respective line of treatment n (%)	115 (12.9%)	29 (4.9%)
Patient deceased prior to respective line of treatment n (%)	156 (17.4%)	23 (3.9%)

N: Number of patients enrolled for first-line treatment.
Potential: Patients with ongoing previous line of treatment or on drug holiday, but still under observation within MYRIAM ("potential for next-line treatment").

Figure 1: First-line treatment (non-SCT): Frequencies of protocols over time (n=894)

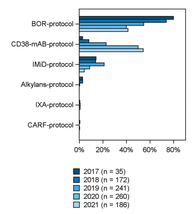


Figure 2: irst-line treatment (SCT induction): Frequencies of protocols over time (n=575)

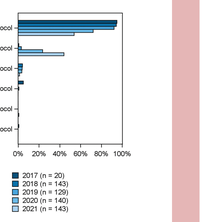


Figure 3: First-line treatment (non-SCT): Best response (n=632)

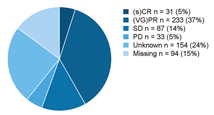
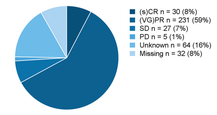


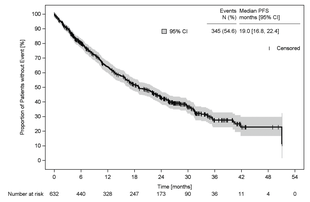
Figure 4: First-line treatment (SCT induction): Best response (n=389)



(s)CR: stringent complete reponse | (VG)PR: (very good) partial response | SD: stable disease | PD: progressive disease.

Best response is documented as "unknown" e.g. when a patient dies unexpectedly during treatment or treatment duration was very short for other reasons (e.g. discontinued due to toxicity) and therefore no tumor assessment was performed.

Figure 5: First-line treatment (non-SCT): Progression-free survival (PFS) from start of first line



Patients with start of first-line treatment at least two years prior to database cut ("outcome sample").

CI: confidence interval
OS: overall survival.

Figure 6: First-line treatment (planned SCT): Progression-free survival (PFS) from start of first line

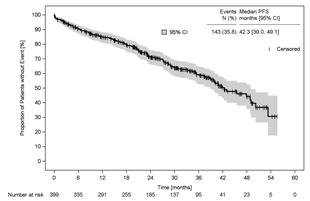


Figure 7: First-line treatment (non-SCT): Overall survival (OS) from start of first line

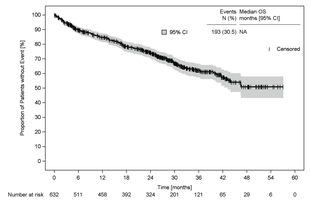
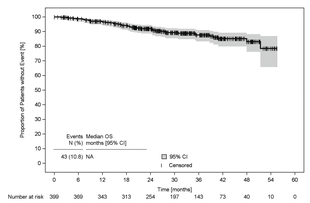


Figure 8: First-line treatment (planned SCT): Overall survival (OS) from start of first line



Abbreviations:

CI: confidence interval | CD: cluster of differentiation | ECOG: Eastern Cooperative Oncology Group | IMiD: imunomodulatory drug | mAB: monoclonal antibody | MM: multiple myeloma | OS: overall survival | PFS: progression-free survival | SCT: stem cell transplantation,

(s)CR: stringent complete reponse | (VG)PR: (very good) partial response | SD: stable disease | PD: progressive disease.

BOR: bortezomib | CARF: carfilzomib | CYC: cyclophosphamide | DARA: daratumumab | Dexa: dexamethasone | ELO: elotuzumab | IXA: ixazomib | LEN: lenalidomide.

Literature:

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649–55.

Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011 Mar 15;173(6):676–82.

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Definition of regimens and treatment protocols:

In MYRIAM all drugs given are documented individually not as pre-defined protocols, and treatment regimens are coded prior to analyses. This allows analyses of frequencies of drugs independent of the regimen used (e.g. CARF) as well as of specific regimens (e.g. Kd) or treatment protocols (e.g. CARF-protocols). For the analysis of treatment protocols the coded regimens were grouped according to the following rule: 1. CD38-containing, 2. elotuzumab-containing, 3. carfilzomib-containing, 4. bortezomib-containing but no daratumumab, 5. ixazomib-containing, 6. alkylating agents-containing [cyclophosphamide, bendamustine, non-HD-melphalan], 7. immunomodulating agents-containing [pomalidomide, lenalidomide, thalidomide] but not in combination with the previously listed drugs. This protocol classification follows GMMG/DSMM expert standard.

Transplantation eligibility:

In MYRIAM no data on SCT eligibility are directly collected but rather whether an SCT was planned and if it was performed. Therefore, SCT patients are no equal to transplant eligible patients, but rather a subgroup of the latter.

Conflicts of interest, general:

MYRIAM is designed, managed and analyzed by iOMEDICO and receives continuous financial support from Amgen GmbH, Celgene - A Bristol-Myers Squibb Company, GlaxoSmithKline Research and Development Limited, and Janssen-Cilag GmbH. None of the funders had any role in study design, data collection and analysis, interpretation of results, decision to publish, or preparation of the abstract.

Conflicts of interest, personal:

Einsele, Hermann Advisory Role or Expert Testimony: BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis; Honoraria: BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis; Other Financial Relationships: BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis

Kiewe, Philipp Advisory Role or Expert Testimony: BMS, Roche, Janssen, Amgen, BeiGene; Honoraria: Novartis

Groschek, Matthias Employment or Leadership Position: Co-Owner of private practise: MVZ Onkologie Groschek-Keller, Co-Owner of Clinical Research Stolberg GmbH, Leader of „onkologisches Zentrum am Bethlehem" (Bethlehem Gesundheitszentrum gGmbH, Steinfeldstr. 5, 52222 Stolberg); Advisory Role or Expert Testimony: Roche Pharma, BMS, IPSEN, GSK; Honoraria: Lecture Fees: BMS / IPSEN / GSK, Congress & travel support: Roche Pharma, Ipsen, Onkovis, Gilead; Financing of Scientific Research: Roche Pharma, BMS, Novartis, Pfizer, ioMedico, Pierre Fabre, Amgen, Astra Zeneca, Sanofi, Medac, Octapharma, Gilead, Merck

Bürkle, Dieter Employment or Leadership Position: Praxisinhaber; Honoraria: Merck, Novartis

von der Heyde, Eyck Employment or Leadership Position: Partner in der onkologischen Praxis am Raschplatz; Honoraria: BMS, Novartis, Iomedico, AstraZeneca; Financing of Scientific Research: Aufwendungen für NIS: Novartis, BMS, Boehringer, AstraZeneca, IG-Vena

Hansen, Timon Advisory Role or Expert Testimony: Amgen, BMS/Celgene, GSK, Janssen, Karyopharm, Oncopeptides, Sanofi, Sobi, Takeda; Honoraria: Alnylam, Amgen, BMS/Celgene, GSK, Janssen, Karyopharm, Oncopeptides, Pfizer, Sanofi, Takeda

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Langer, Christian Employment or Leadership Position: no; Advisory Role or Expert Testimony: Vortrag/Teilnahme Advisory Board: AstraZeneca, GSK plc , Bristol Myers Squibb, Roche.

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Potthoff, Karin Employment or Leadership Position: Führungsposition iOMEDICO

Medinger, Tanja Employment or Leadership Position: Angestellt bei iOMEDICO

Engelhardt, Monika Other Financial Relationships: geringe Studiendokugelder an UKF Med 1 Abteilung (Prof. Duyster)

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